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Botulism and Picrotoxin.

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Two phases are differentiated in botulinal intoxication: (1) a period of stimulation and (2) of respiratory depression. Experiments with picrotoxin point to reciprocal potentiation during the phase of botulinal stimulation and antagonism during the phase of depression.

The botulinal toxin (type A) in these experiments was prepared and supplied by the National Institute of Health in Washington. Its potency was expressed in terms of an intravenous mouse MLD, one unit being 0.00005 cc, the smallest amount that would kill a 17 to 20 g mouse when injected intravenously.

These experiments were performed on healthy stock rabbits ranging in weights from 1.45 to 1.85 kg.

Injected into the marginal ear vein 10,000 U (0.5 cc) of the toxin caused death (100%) within 13 hours average time. Three mg of picrotoxin intravenously administered is surely convulsant and frequently lethal; 2 mg is usually convulsant but non-lethal; while 1 mg is never lethal, rarely convulsant but regularly hyperstimulating to normal rabbits within this weight-range. However, when within the first hour following the injection of botulinal toxin, 3 mg, 2 mg, or 1 mg of picrotoxin was injected into the vein or even the muscle all the animals died within the first 2 hours with severe convulsions. But when an interval of 3 to 5 hours was allowed to elapse between the time of injection of toxin and picrotoxin with the picrotoxin divided into 0.1 mg doses each hour, sub-

TABLE I.

Controls		Treated (early)		Treated (delayed)	
Dose	Life Span, hr	Picrotoxin	Life Span, hr	Picrotoxin	Life Span, hr
a. Intravenous		(Within the first hour)		(3-5 hr after)	
(1) 10,000 U	13	3 mg—intramuscularly	1.1	0.1 mg/hr subcut.	20
(2) ,, ,,	14	2 ,, ,,	1.2	,, ,, ,,	23
(3) ,, ,,	12	1 ,, ,,	1.4	,, ,, ,,	22
(4) ,, ,,	13	1 ,,—intravenously	0.5	,, ,, ,,	19
b. Intraäbdominal		(1 hr later)		(3 hr later)	
(1) 20,000 U	5.5	1 mg—intravenously	1.7	0.1 mg/hr subcut.	18.0
(2) 40,000 U	4.9	1 ,, ,,	0.9	,, ,, ,,	15.3
(3) 60,000 U	4.8	1 ,, ,,	1.2	,, ,, ,,	14.5
c. Intravenous		(1 hr later)		(1 hr later)	
(1) 20,000 U	2.4	1 mg—subcutaneously	5	0.2 mg/hr subcut.	7.0
(2) 40,000 U	1.6	1 ,, ,,	3.2	,, ,, ,,	3.4
(3) 60,000 U	1.4	1 ,, ,,	1.3	,, ,, ,,	5.4

cutaneously, the life span was extended from an average of 13 (controls) to 23 hours. (Table I-a.)

Intraäbdominally, 20,000 U, 40,000 U, and 60,000 U, each of botulinal toxin was 100% lethal in 5 hours (average time). When administered by this route and in these amounts there began to appear signs of intoxication between the second and the third hour. When an interval of 3 hours was allowed to elapse and 0.1 mg of picrotoxin was given per hour, subcutaneously, the life span was increased from 5 hours (controls) to 15.9 hours. (Table I-b.)

Intravenously 20,000 U, 40,000 U, and 60,000 U, of botulinal toxin were in the aggregate 100% lethal in 1.8 hours, the signs of intoxication being in evidence within the first 50 minutes. When 1 mg picrotoxin was administered subcutaneously one hour after the botulinal toxin the life span was extended to 3 hours. Better still, when the dose of picrotoxin was given as 0.2 mg each hour, subcutaneously, the life span was extended to 5.2 hours. (Table I-c.)

Small intravenous injections (10,000 U) and large intraäbdominal (20,000 U, 40,000 U, and 60,000 U) injections of botulinal toxin produce a slow toxemia characterized by restlessness, manifest discomfort, listlessness interrupted by "fits and starts", jerky irregular respiration, definite dyspnea, gasping, falling over, very slow respiration, and death.

Large intravenous doses (20,000 U, 40,000 U, and 60,000 U) produce rapid toxemia in which one observes hyperexcitability, manifest discomfort, dyspnea, gasping, falling over, and death in profound depression. In spite of the gradualness as against the rapidity of appearance of the symptoms in the 2 groups, both exhibit evidences of the 2 distinct phases, *viz.*, (1) stimulation, (2) depression. The second phase is ushered in by displays of manifest discomfort. The animal seems unable to remain quietly for any length of time in one place. Between intervals of quiet he jumps about as though the air in his environment is being shut off. This marks the period of transition.

If picrotoxin is given during the phase of stimulation its convulsant action is markedly increased so that a dose which would ordinarily be sub-threshold to convulsions may become a fatally convulsant dose. Here the 2 poisons definitely potentiate each other. If, however, picrotoxin is administered during the period of transition or early in the phase of depression they antagonize each other so that the impending embarrassment to the respiratory center is delayed.

The high mortality in botulinal poisoning is indicative of the limitation of our knowledge in handling this grave, but fortunately uncommon, condition. Bronfenbrenner and Weiss[1] discovered that

[1] Bronfenbrenner, J. J., and Weiss, H., *J. Exp. Med.*, 1924, **39**, 517.

certain depressants so extended the latent period of the poison that the employment of antitoxin could be postponed for hours provided that the animal was kept under the influence of ether anesthesia, luminal, nitrous oxide-oxygen or morphine. In acute poisoning delay is always desirable. Picrotoxin administered during the phase of stimulation in botulinal intoxication enhances the toxicity of the latter; but administered at intervals during the transition or the depressed phase in small amounts it antagonizes the toxic action of botulinus and delays the terminal event.